

American College of Rheumatology Guidelines for Screening, Treatment, and Management of Lupus Nephritis

BEVRA H. HAHN,¹ MAUREEN A. McMAHON,¹ ALAN WILKINSON,[†] W. DEAN WALLACE,¹ DAVID I. DAIKH,² JOHN D. FITZGERALD,¹ GEORGE A. KARPOUZAS,¹ JOAN T. MERRILL,³ DANIEL J. WALLACE,⁴ JINOOS YAZDANY,² ROSALIND RAMSEY-GOLDMAN,⁵ KARANDEEP SINGH,¹ MAZDAK KHALIGHI,¹ SOO-IN CHOI,¹ MANEESH GOGIA,¹ SUZANNE KAJAJA,¹ MOHAMMAD KAMGAR,¹ CHRISTINE LAU,¹ WILLIAM J. MARTIN,¹ SEFALI PARIKH,¹ JUSTIN PENG,¹ ANJAY RASTOGI,¹ WEILING CHEN,¹ AND JENNIFER M. GROSSMAN¹

Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to these guidelines and recommendations to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed or endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice.

The American College of Rheumatology is an independent, professional, medical and scientific society which does not guarantee, warrant, or endorse any commercial product or service.

Introduction

In the US, approximately 35% of adults with systemic lupus erythematosus (SLE) have clinical evidence of nephritis at the time of diagnosis, with an estimated total of 50–60% developing nephritis during the first 10 years of disease (1–4). The prevalence of nephritis is significantly

higher in African Americans and Hispanics than in whites, and is higher in men than in women. Renal damage is

¹Bevra H. Hahn, MD, Maureen A. McMahon, MD, W. Dean Wallace, MD, John D. Fitzgerald, MD, George A. Karpouzas, MD, Karandeep Singh, MD, Mazdak Khalighi, MD, Soo-In Choi, MD, Maneesh Gogia, MD, Suzanne Kafaja, MD, Mohammad Kamgar, MD, Christine Lau, MD, William J. Martin, MD, Sefali Parikh, MD, Justin Peng, MD, Anjay Rastogi, MD, PhD, Weiling Chen, MA, Jennifer M. Grossman, MD: University of California, Los Angeles; ²David I. Daikh, MD, Jinoos Yazdany, MD, MPH: University of California, San Francisco; ³Joan T. Merrill, MD: Oklahoma Medical Research Foundation, Oklahoma City; ⁴Daniel J. Wallace, MD: Cedars-Sinai Medical Center, University of California, Los Angeles; ⁵Rosalind Ramsey-Goldman, MD, DrPH: Northwestern University, Chicago, Illinois.

[†]Dr. Wilkinson is deceased.

Dr. Hahn has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from UCB and Abbott, and has served on the Data and Safety Monitoring Board for Anthera. Dr. McMahon has received speaking fees

(more than \$10,000) from HGS/GSK. Dr. Merrill has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from UCB, Amgen, Pfizer, Lilly, Bristol-Myers Squibb, Genentech/Roche, EMD Serono, Neovacs, Cephalon, MedImmune, Questcor, Argos, Abbott, Ono, Astellas, Baxter, RPS, and Takeda, and (more than \$10,000 each) from Human Genome Sciences/GlaxoSmithKline and Parxel, and has served on the Data and Safety Monitoring Board and/or Adjudication for Industry Trials for Amgen, Celgene, and Pfizer. Dr. Rastogi has received consultant fees, speaking fees, and/or honoraria (more than \$10,000 each) from ViiV, Novartis, Genzyme, and Cubist.

Members of the Task Force Panel: Jo H. M. Berden, Jill P. Buyon, Gabriel Contreras, Karen H. Costenbader, Mary Anne Dooley, Peng Thim Fan, Rosalind Ramsey-Goldman, Frederic A. Houssiau, David A. Isenberg, Kenneth C. Kalunian, Susan Manzi, Chi-Chiu Mok, Liz Shaw-Stabler, Brad Rovin, Murray B. Urowitz, and David Wofsy.

Address correspondence to Bevra H. Hahn, MD, University of California, Los Angeles, School of Medicine, Room 32-48 Rehabilitation Building, Box 951670, Los Angeles, CA 90095-1670. E-mail: bhahn@mednet.ucla.edu.

Submitted for publication June 15, 2011; accepted in revised form March 5, 2012.

more likely to develop in nonwhite groups (1–4). Overall survival in patients with SLE is approximately 95% at 5 years after diagnosis and 92% at 10 years after diagnosis (5,6). The presence of lupus nephritis (LN) significantly reduces survival to approximately 88% at 10 years, with even lower survival in African Americans (5,6).

The American College of Rheumatology (ACR) last published guidelines for management of SLE in 1999 (7). That publication was designed primarily for education of primary care physicians and recommended therapeutic and management approaches for many manifestations of SLE. Recommendations for management of LN consisted of pulse glucocorticoids followed by high-dose daily glucocorticoids in addition to an immunosuppressive medication, with cyclophosphamide (CYC) viewed as the most effective immunosuppressive medication for diffuse proliferative glomerulonephritis. Mycophenolate mofetil (MMF) was not yet in use for LN and was not mentioned. Since that time, many clinical trials of glucocorticoids plus immunosuppressive interventions have been published, some of which are high-quality prospective trials, and some that are not only prospective but also randomized. Therefore, the ACR determined that a new set of management recommendations was in order. A combination of an extensive literature review and the opinions of highly-qualified experts, including rheumatologists, nephrologists, and pathologists, has been used to reach the recommendations. The management strategies discussed here apply to LN in adults, particularly to those receiving care in the US, and include interventions that were available in the US as of February 2012.

While these recommendations were developed using rigorous methodology, guidelines do have inherent limitations in informing individual patient care; hence, the selection of the term “recommendations.” While they should not supplant clinical judgment or limit clinical judgment, they do provide expert advice to the practicing physician managing patients with LN.

Methods

A modified RAND/University of California at Los Angeles (UCLA) Appropriateness Method, summarized in Figure 1, was used to develop these recommendations (8). This method uses a combination of a systematic literature review and expert opinion. A Core Executive Panel, in conjunction with the Working Group, reviewed the existing guidelines, refined the domains of the project, performed a systematic literature review, and developed clinical scenarios. Votes of the Task Force Panel on the appropriateness of interventions in the various scenarios determined the recommendations. Similar methodology was used to prepare recent ACR recommendations for the management of glucocorticoid-induced osteoporosis (9) and for the use of nonbiologic and biologic therapies in patients with rheumatoid arthritis (10).

A systematic review was performed with the assistance of a UCLA research librarian. The search strategy is outlined in the Evidence Report (available in the online version of this article at <http://onlinelibrary.wiley.com/>

[journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)), and briefly, we used Medline (through PubMed) by applying medical subject headings and relevant keywords with references from January 1, 1966, through January 22, 2010, for all literature with the term “lupus kidney diseases” published in English. The search was updated on August 8, 2010, and clinical trials and meta-analyses published after that date were reviewed by the corresponding author (BHH) in April 2011 and February 2012. The articles were divided among review teams, each comprised of a junior fellow and a senior mentor. Articles were screened to eliminate reviews, opinion articles, cohort studies that did not include patients 18 years of age or older, cohorts or prospective trials containing fewer than 29 patients, studies not requiring patients to meet a preestablished definition of SLE or LN, or studies with less than 6 months of followup data. The authors examined each publication, and only the most recent or complete report of a clinical trial was incorporated when duplicate reports were found. The remaining cohort articles and all prospective randomized clinical trials were reviewed in full. Of the studies selected for full review, the 2 reviewers independently reviewed the articles, and then conferred to reach agreement on the description of each study assigned to them. Tables were composed, including summaries of results, descriptions of patients studied (cohorts in one table and prospective clinical trials in another), therapeutic interventions, and outcomes for each study selected. The Working Group met weekly to review progress; the Core Executive Panel met monthly by teleconference. The 2 committees wrote an Evidence Report (available in the online version of this article at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)) to summarize the literature review.

Using the Evidence Report and expertise of the Core Executive Panel members, clinical scenarios were constructed. These scenarios (provided in detail in the Evidence Report, available in the online version of this article at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)) were voted on by the Task Force Panel to elicit opinions on the appropriateness regarding decisions involving case definition, renal biopsy and histology, treatments, outcomes, and monitoring. The scenarios included indications for a renal biopsy; laboratory monitoring of LN; induction treatment options for International Society of Nephrology/Renal Pathology Society (ISN/RPS) class II, class III/IV with and without crescents, and class V membranous LN; and thrombotic thrombocytopenic purpura. Maintenance therapy, treatment for refractory disease, management of nephritis during pregnancy, and management of comorbid conditions associated with nephritis itself and immunosuppression from treatments (i.e., hypertension, hypercholesterolemia, and pneumocystis prophylaxis) were also incorporated into scenarios. While steroid dosing and tapering were recognized to be important aspects of LN management, the Core Expert Panel could not reach a consensus on a regimen given the variability inherent in LN; therefore, precise steroid-tapering schedules were not included in the scenarios. Likewise, definitions of response, degree of response, flare, severity of flare, and remission vary significantly in the literature and depend on the starting point in each individual pa-

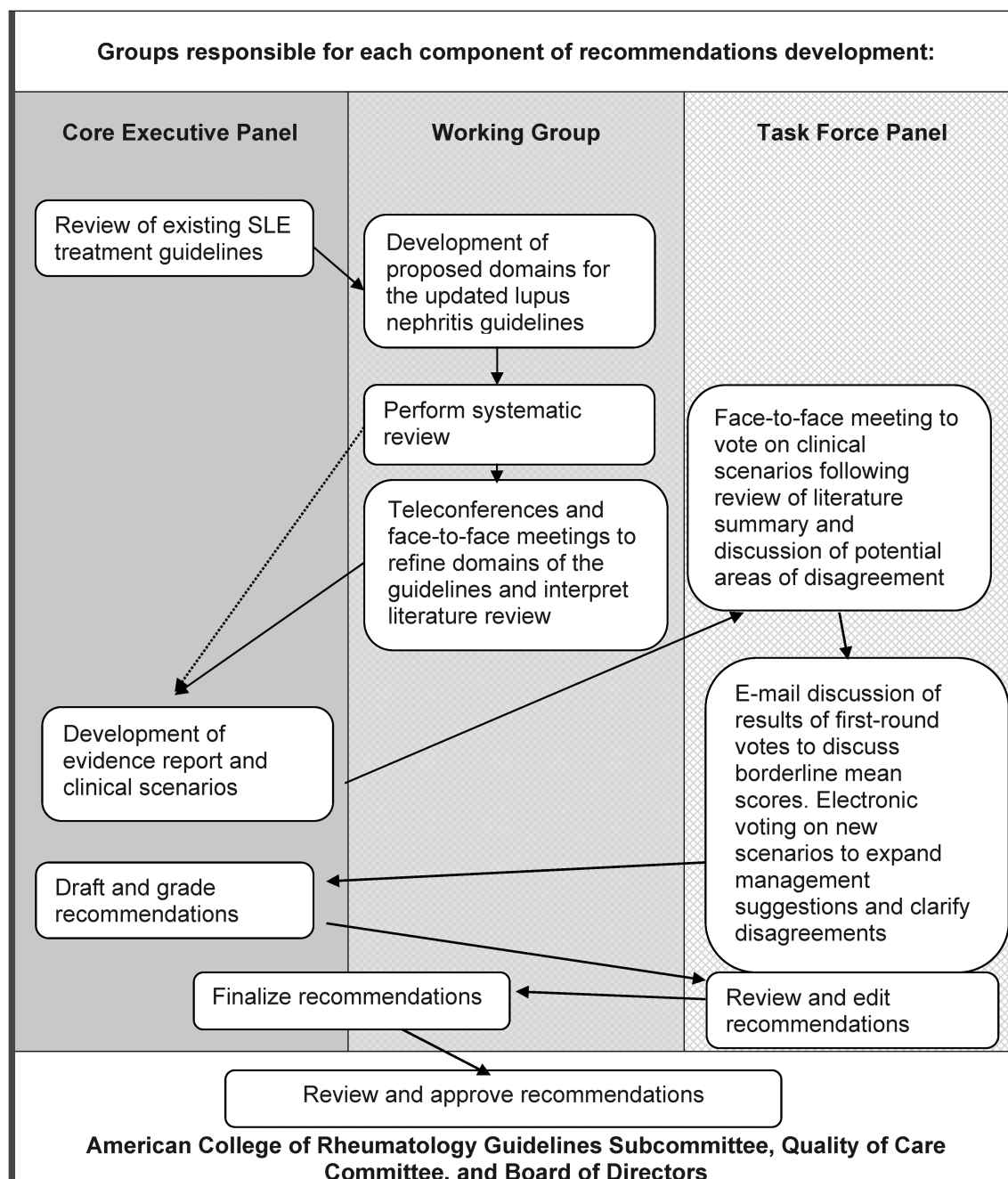


Figure 1. Flow chart of groups responsible for each component of recommendations development. SLE = systemic lupus erythematosus.

tient; therefore, an exact definition of these terms was not included in the scenarios. Identification of response, flare, and failure to respond were based on the experienced clinician's opinion, and it is intended that the treating clinician make similar judgments in employment of the recommendations outlined here. The Core Expert Panel agreed that specific therapy was not indicated for class I or class II renal biopsies; therefore, scenarios and recommendations were not created for these histologic classifications.

The Evidence Report, including search strategies, abstraction tools, and case scenarios, as well as summaries of the literature for randomized controlled trials (RCTs)

and cohort studies, were submitted to members of the Task Force Panel prior to their face-to-face meeting, which was held in November 2010 in Atlanta, Georgia. (These reports are available in the online version of this article at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).) Each member of the Task Force Panel voted on each scenario using a 9-point Likert scale, where a vote of 1 meant not valid and 9 meant extremely valid. The results of the first round of voting were presented anonymously and discussed at the face-to-face meeting. At the conclusion of the meeting, a second round of voting occurred, with the results of this round informing the development

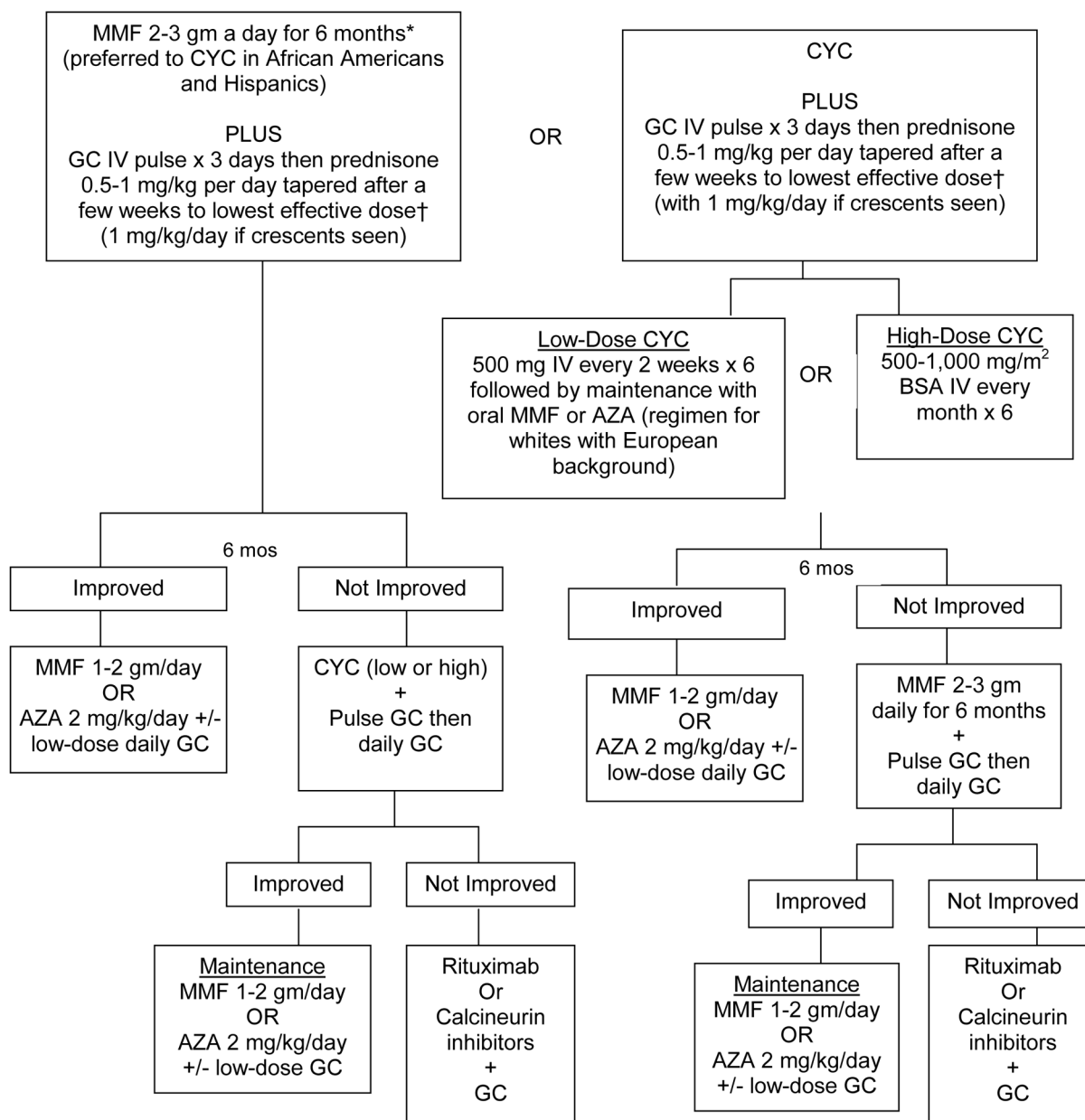


Figure 2. Class III/IV induction therapy. MMF = mycophenolate mofetil; * = the Task Force Panel discussed their preference of MMF over cyclophosphamide (CYC) in patients who desire to preserve fertility; GC = glucocorticoids; IV = intravenous; † = recommended background therapies for most patients are discussed in section III in the text; AZA = azathioprine; BSA = body surface area.

of the final recommendations. After the meeting, members of the Core Executive Panel tallied the votes. Agreement was defined as not more than 2 votes outside of the 3-point range in which the median vote falls. A recommendation was made both when there was agreement and when the median vote fell in the 7–9 range. Members of the Core Executive Panel reviewed the tally and identified areas of agreement or disagreement that were not compatible with current therapeutic recommendations or opinions in the recent literature. New scenarios to clarify such issues were constructed, and members of the Task Force Panel voted on the new scenarios. The results of the voting are shown in Figures 2–4. They are also shown by italicized lettering in the text.

The strength of the evidence was graded using the method reported by the American College of Cardiology (11) and used in the previous ACR recommendations articles (9,10). Level A evidence represents data derived from multiple RCTs or a meta-analysis, level B evidence represents data from a single RCT or nonrandomized study, and level C evidence represents data from consensus, expert opinion, or case series.

Based on those results, this document was written, containing recommendations for treatment and monitoring of LN, and distributed to all members of each panel for comments and editing. Thereafter, the completed documents were submitted to the ACR for review and approval by the ACR Guidelines Subcommittee, ACR Quality of Care Com-

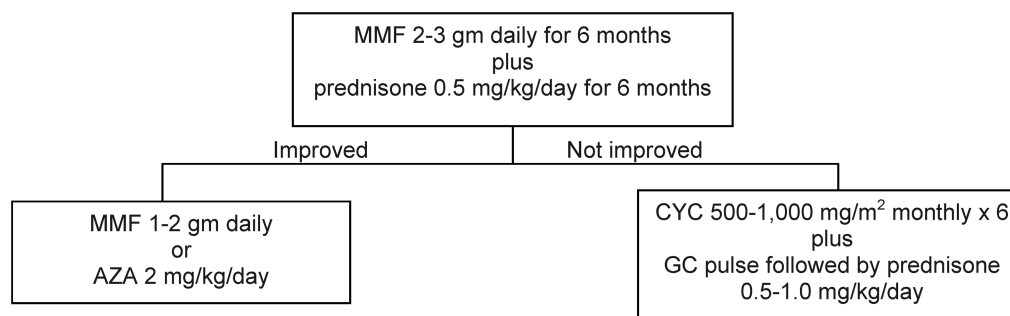


Figure 3. Treatment of class V without proliferative changes and with nephrotic range proteinuria (>3 gm/24 hours). Recommended background therapies for most patients are discussed in section III in the text. MMF = mycophenolate mofetil; AZA = azathioprine; CYC = cyclophosphamide; GC = glucocorticoids.

mittee, and ACR Board of Directors. The final document appears here.

I. Case Definition for LN

For the purpose of these recommendations, LN is defined as clinical and laboratory manifestations that meet ACR criteria (persistent proteinuria >0.5 gm per day or greater than 3+ by dipstick, and/or cellular casts including red blood cells [RBCs], hemoglobin, granular, tubular, or mixed) (12). A review of the ACR criteria has recommended that a spot urine protein/creatinine ratio of >0.5 can be substituted for the 24-hour protein measurement, and “active urinary sediment” (>5 RBCs/high-power field [hpf], >5 white blood cells [WBCs]/hpf in the absence of infection, or cellular casts limited to RBC or WBC casts) can be substituted for cellular casts (1). An additional, perhaps optimal, criterion is a renal biopsy sample demonstrating immune complex-mediated glomerulonephritis compatible with LN (1). Finally, for the purpose of implementing these recommendations, the Core Executive Panel agreed that a diagnosis of LN should also be considered valid if based on the opinion of a rheumatologist or nephrologist.

II. Renal Biopsy and Histology

The Task Force Panel recommended that all patients with clinical evidence of active LN, previously untreated, undergo renal biopsy (unless strongly contraindicated) so

that glomerular disease can be classified by current ISN/RPS classification (level C evidence) (13,14) (Table 1). In addition, disease can be evaluated for activity and chronicity and for tubular and vascular changes (15). Finally, biopsies may identify additional or alternative causes of renal disease, such as tubular necrosis related to medications, hypovolemia, or hypotension. Biopsy is most highly recommended in patients with the characteristics indicated in Table 2.

The Task Force Panel recommended that treatment be based in large part on the classification of type of LN by these ISN/RPS criteria (13–15). As a result, the following recommendations are presented according to the histologic classification of nephritis. *The Task Force Panel agreed that class I* (minimal mesangial immune deposits on immunofluorescence with normal light microscopy) *and class II* (mesangial hypercellularity or matrix expansion on light microscopy with immune deposits confined to mesangium on immunofluorescence) *generally do not require immunosuppressive treatment (level C evidence).* In general, patients with class III (subendothelial immune deposits and proliferative changes in $<50\%$ of glomeruli) and class IV (subendothelial deposits and proliferative glomerular changes involving $\geq 50\%$ of glomeruli) require aggressive therapy with glucocorticoids and immunosuppressive agents. Class V (subepithelial immune deposits and membranous thickening of glomerular capillaries) when combined with class III or IV should be treated in the

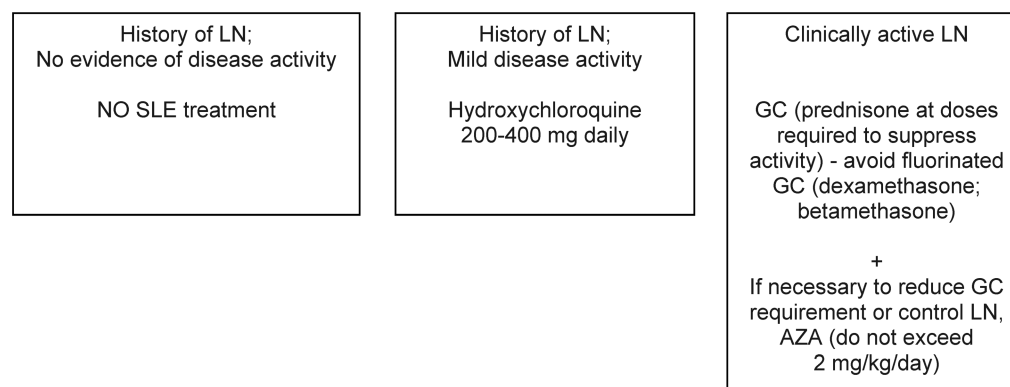


Figure 4. Treatment of class III, IV, and V in patients who are pregnant. LN = lupus nephritis; SLE = systemic lupus erythematosus; GC = glucocorticoids; AZA = azathioprine.

Table 1. International Society of Nephrology/Renal Pathology Society 2003 classification of LN*

Class I	Minimal mesangial LN
Class II	Mesangial proliferative LN
Class III	Focal LN (<50% of glomeruli) III (A): active lesions III (A/C): active and chronic lesions III (C): chronic lesions
Class IV	Diffuse LN ($\geq 50\%$ glomeruli) Diffuse segmental (IV-S) or global (IV-G) LN IV (A): active lesions IV (A/C): active and chronic lesions IV (C): chronic lesions
Class V	Membranous LN†
Class VI	Advanced sclerosing LN ($\geq 90\%$ globally sclerosed glomeruli without residual activity)

* Adapted, with permission, from ref. 15. LN = lupus nephritis.
† Class V may occur in combination with class III or IV, in which case both will be diagnosed.

same manner as class III or IV. Class V alone (“pure membranous LN”) may be approached somewhat differently, as indicated below in section VI. Histologic class VI (sclerosis of $\geq 90\%$ of glomeruli) generally requires preparation for renal replacement therapy rather than immunosuppression. The designations “A” and “C” indicate whether active or chronic changes are present; the higher the chronicity the less likely that the nephritis will respond to immunosuppression (15,16). However, A or C classifications were not included in the entry criteria for clinical trials in LN published to date, and therefore they are not considered in the recommendations.

III. Adjunctive Treatments

The Task Force Panel recommended that all SLE patients with nephritis be treated with a background of hydroxychloroquine (HCQ; level C evidence), unless there is a contraindication. This opinion was based on a prospective

controlled trial (17) showing that flare rates of lupus are lower in SLE patients continuing HCQ compared to those who switched to placebo, and on recent cross-sectional and prospective data (18,19) showing significantly lower damage accrual, including renal damage, in SLE patients receiving HCQ. In addition, HCQ treatment may reduce the risk of clotting events in SLE (20,21).

All LN patients with proteinuria ≥ 0.5 gm per 24 hours (or equivalent by protein/creatinine ratios on spot urine samples) should have blockade of the renin-angiotensin system, which drives intraglomerular pressure (level A evidence for nondiabetic chronic renal disease). Treatment with either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) reduces proteinuria by approximately 30%, and significantly delays doubling of serum creatinine and progression to end-stage renal disease in patients with nondiabetic chronic renal disease (22). These classes of medications are contraindicated in pregnancy. The use of combination ACE inhibitors/ARB therapies is controversial (23). ACE inhibitors or ARB treatments are superior to calcium-channel blockers and diuretics alone in preserving renal function in chronic kidney disease (24).

The Task Force Panel recommended that careful attention be paid to control of hypertension, with a target of $\leq 130/80$ mm Hg (level A evidence for nondiabetic chronic renal disease). The recommendation is based on prospective trials and meta-analyses showing that observing this target is associated with a significant delay in progression of renal disease, compared to higher targets or inadequate blood pressure control (22). *The Task Force Panel also recommended that statin therapy be introduced in patients with low-density lipoprotein cholesterol >100 mg/dl (level C evidence) (25).* Note that a glomerular filtration rate <60 ml/minute/1.73 m² (equivalent to a serum creatinine level >1.5 mg/dl or 133 μ moles/liter) is a risk factor for accelerated atherosclerosis (22). SLE itself is also an independent risk factor for accelerated atherosclerosis (26).

Finally, the Task Force Panel recommended that women of child-bearing potential with active or prior LN receive counseling regarding pregnancy risks conferred by the disease and its treatments (level C evidence).

Table 2. Indications for renal biopsy in patients with systemic lupus erythematosus*

	Level of evidence
Increasing serum creatinine without compelling alternative causes (such as sepsis, hypovolemia, or medication)	C
Confirmed proteinuria of ≥ 1.0 gm per 24 hours (either 24-hour urine specimens or spot protein/creatinine ratios are acceptable)	C
Combinations of the following, assuming the findings are confirmed in at least 2 tests done within a short period of time and in the absence of alternative causes: a. Proteinuria ≥ 0.5 gm per 24 hours plus hematuria, defined as ≥ 5 RBCs per hpf b. Proteinuria ≥ 0.5 gm per 24 hours plus cellular casts	C

* RBCs = red blood cells; hpf = high-power field.

IV. Recommendations for Induction of Improvement in Patients With ISN Class III/IV Lupus Glomerulonephritis

The Task Force Panel recommended MMF (2–3 gm total daily orally) or intravenous (IV) CYC along with glucocorticoids (level A evidence) (Figure 2). MMF and CYC are considered equivalent based on recent high-quality studies, a meta-analysis, and expert opinion (27–32). Long-term studies with MMF are not as abundant as those with CYC; data show good results for induction therapy with MMF of 3 gm total dose daily for 6 months, followed by maintenance with lower doses of MMF for 3 years (32). MMF has been similar in efficacy in all races studied to date (whites, Asians, African Americans, and Latin/Hispanic Americans). The Aspreva Lupus Management Study (ALMS) trial comparing response rates of LN to MMF plus

glucocorticoids showed similar improvement in whites, Asians, and other races (primarily African Americans and Hispanics). However, *the Task Force Panel voted that Asians compared to non-Asians might require lower doses of MMF for similar efficacy (level C evidence)*. Therefore, the physician might aim for 3 gm per day total daily highest dose in non-Asians and 2 gm per day in Asians. A recent study (33) reported good responses in Taiwanese treated with these lower doses. There is evidence that African Americans and Hispanics with LN respond less well to IV CYC than do patients of white or Asian races (27,34,35). MMF/mycophenolic acid (MPA) may be an initial choice more likely to induce improvement in patients who are African American or Hispanic (35).

The exact suggested dose of MMF varied based on the clinical scenario: for those with class III/IV without cellular crescents and for those with proteinuria and a stable creatinine for whom a renal biopsy sample cannot be obtained, both 2 gm and 3 gm total daily doses were acceptable to the Task Force Panel, while a dose of 3 gm daily was favored for those with class III/IV and crescents and for those with proteinuria and a recent significant rise in creatinine.

Some evidence suggests that MPA and enteric-coated mycophenolate sodium are less likely than MMF to cause nausea and diarrhea, but this is controversial, and the exact equivalency of the preparations is not firmly established (36,37). Studies using these other MMF preparations are in progress. *The Core Expert Panel recommended that MMF and MPA are likely to be equivalent in inducing improvement of LN, with 1,440–2,160 mg total daily dose of MPA roughly equivalent to 2,000–3,000 mg total daily dose of MMF*. Some investigators (38) have suggested that serum levels of MPA, the active metabolite of MMF, should be measured at the trough or peak (1 hour after a dose), and treatment of SLE should be guided by these levels. However, there are not enough data at this time to make recommendations for monitoring of drug levels.

There are 2 regimens of IV CYC recommended by the Task Force Panel: 1) low-dose “Euro-Lupus” CYC (500 mg IV once every 2 weeks for a total of 6 doses), followed by maintenance therapy with daily oral azathioprine (AZA) or daily oral MMF (level B evidence), and 2) high-dose CYC (500–1,000 mg/m² IV once a month for 6 doses), followed by maintenance treatment with MMF or AZA (level A evidence) (39–41) (Figure 2). Previous studies suggested that 30 months of high-dose IV CYC (the “National Institutes of Health” regimen [42–44]) in which CYC was given monthly for 6 doses, then quarterly for an additional 2 years, was more effective in preventing renal flare than the shorter 6-month regimen. However, the more current 3- to 6-month regimens followed by AZA or MMF maintenance are showing good long-term results (32,45,46). Limited prospective trials comparing daily oral CYC to the high-dose IV therapy have shown near equivalence in efficacy and toxicity (47,48). *If CYC is being considered for treatment, the Core Expert Panel recommended IV CYC at the low “Euro-Lupus” dose for white patients with Western European or Southern European racial/ethnic backgrounds (level B evidence).* In those European study patients, the low- and high-dose regimens

were equivalent in efficacy (40,41), and serious infections were less frequent with the lower doses. The low- and high-dose regimens have not been compared in nonwhite racial groups. Ten years of followup comparing low- and high-dose regimens showed similar rates of LN flares, end-stage renal disease, and doubling of the serum creatinine (40).

Pulse IV glucocorticoids (500–1,000 mg methylprednisolone daily for 3 doses) in combination with immunosuppressive therapy is recommended by the Task Force Panel, followed by daily oral glucocorticoids (0.5–1 mg/kg/day), followed by a taper to the minimal amount necessary to control disease (level C evidence). The recommendation of initiating induction therapy with pulse glucocorticoids is based primarily on expert opinion; some recent prospective trials have employed pulse steroids at the onset of treatment (750 mg methylprednisolone daily $\times$ 3 [41]), whereas others have not (27,29,30). There are insufficient data to recommend a specific steroid taper because the nephritis and extrarenal manifestations vary from patient to patient. There was no consensus reached regarding the use of monthly IV methylprednisolone with monthly IV CYC. An extended followup study has suggested benefit of the combination of monthly IV methylprednisolone and IV CYC over IV CYC alone (49).

Although AZA has been used to treat LN, the Task Force Panel did not recommend it as one of the first choices for induction therapy. AZA treatment to induce improvement was less effective than CYC combined with standard glucocorticoid doses in one study (42). Over the long term (1–5 years of treatment), AZA as an induction-plus-maintenance agent was less effective than CYC induction therapy in preventing flares of LN, and CYC was better at delaying progression of chronic lesions on repeat renal biopsies (44,50,51).

The panel recommends that most patients be followed for 6 months after initiation of induction treatment with either CYC or MMF before making major changes in treatment other than alteration of glucocorticoid doses, unless there is clear evidence of worsening at 3 months (50% or more worsening of proteinuria or serum creatinine; level A evidence).

A recent study retrospectively analyzing a high-quality trial showed that after 8 weeks of induction treatment with either CYC or MMF, patients with LN who showed $\geq 25\%$ reduction in proteinuria and/or normalization of C3 and/or C4 serum levels were likely to show good clinical renal responses (52). Similarly, after 6 months of treatment, a decrease in serum creatinine and in proteinuria to < 1 gm per 24 hours predicts a good long-term outcome (53). Approximately 50% of SLE patients with serious LN showed definite improvement in renal parameters after 6 months of treatment with either MMF or CYC (27,29,41), and the proportion of responders increased to 65–80% between 12 and 24 months of treatment (40,41).

Fertility issues are often a concern for young SLE patients with nephritis. In a discussion, the Task Force Panel recommended that MMF was preferable to CYC for patients who express a major concern with fertility preservation, since high-dose CYC can cause permanent infertility in both women and men (level A evidence of gonadal

toxicity) (31,54). In one study (55), women with LN treated with high-dose CYC (500–1,000 mg/m² IV once monthly $\times$ 6, with some treated quarterly for another 18 months) developed sustained amenorrhea related to age: this occurred in 12% of those ages <25 years, in 27% of those ages <30 years, and in 62% of those ages $\geq$ 31 years. Furthermore, when women ages >25 years were treated with 6 months of high-dose IV CYC (cumulative dose 4.4–10 gm), sustained amenorrhea developed in 17% compared to 64% of those treated with the additional quarterly doses. Therefore, 6 months of high-dose IV CYC was associated with approximately 10% sustained infertility in young women, and higher rates in older women. If 6 months of CYC were followed by quarterly doses, there was a higher rate of infertility (42,55). In the Euro-Lupus Nephritis Trial (40,41), 4.5% of patients had menopause in the low-dose arm (CYC 500 mg IV every 2 weeks $\times$ 6, cumulative dose 3 gm) compared to 4.3% in the high-dose arm. The high dose began at 500 mg/m², was adjusted upward according to the WBC nadir, and was administered IV monthly $\times$ 6. The Task Force Panel did not reach a consensus on the use of leuprolide (56) in patients with SLE receiving CYC as a means to preserve fertility. They also noted that MMF is teratogenic (class D in US Food and Drug Administration [FDA] ranking [37]). Therefore, the physician should be sure that a patient is not pregnant before prescribing MMF or MPA, and the medications should be stopped for at least 6 weeks before pregnancy is attempted.

VI. Recommendations for Induction of Improvement in Patients With Class IV or IV/V Plus Cellular Crescents

The Task Force Panel recommended either CYC or MMF for induction of improvement in this type of LN (level C evidence), along with IV pulses of high-dose glucocorticoid and initiation of oral glucocorticoids at the higher-range dosage, 1 mg/kg/day orally (Figure 2). For the purpose of these recommendations statements, the presence of any crescents on a renal biopsy sample was considered crescentic LN. Until recently, experts have favored high-dose IV CYC for treatment of LN with cellular crescents. In general, the presence of crescents indicates a poorer prognosis, even with appropriate treatment (57). One recent retrospective study in China (58) suggested that MMF (1 gm twice daily) is at least as effective as high doses of CYC in crescentic class IV LN. Prospective, international, or North American trials in such patients are not available. Further recommendations for a pregnant patient with crescentic glomerulonephritis are provided in section X.

VI. Recommendations for Induction of Improvement in Patients With Class V “Pure Membranous” LN

The Task Force Panel recommends that patients with pure class V LN and with nephrotic range proteinuria be started on prednisone (0.5 mg/kg/day) plus MMF 2–3 gm total daily dose (level A evidence) (Figure 3). In a retrospective analysis of patients with class V nephritis (59), MMF 2–3 gm total daily dose orally plus daily prednisone (mean 27

mg daily) for 6 months resulted in improvement similar to that with IV CYC (0.5–1.0 mg/kg IV monthly $\times$ 6) plus prednisone, with 0–30% of patients having nephrotic range proteinuria after 6 months.

Other therapies for membranous LN have been reported; however, the Task Force Panel did not reach consensus on a recommendation regarding those therapies. For example, in a prospective trial (60), 3 treatment groups were compared: alternate day prednisone (40 mg/m² orally every other day), tapered after 8 weeks to reach 10 mg/m² by 12 months, or alternate day prednisone plus CYC 500–1,000 mg/m² IV every 2 months for 6 doses, or alternate day prednisone plus cyclosporine 5 mg/kg for 11 months. Remission occurred in 27% of patients receiving prednisone alone, 60% receiving CYC, and 83% receiving cyclosporine by 3–12 months of treatment. After the first year (36 months of followup), renal flares were significantly lower in the CYC group compared to the cyclosporine group.

VII. Recommendations for Maintaining Improvement in Patients Who Respond to Induction Therapy

The Task Force Panel recommended that either AZA or MMF be used for maintenance therapy (level A evidence) (Figure 2). Two recent prospective trials studied maintenance treatment of patients with LN following induction treatments (32,45). In the larger study (32), which had sites in the US, Western Europe, China, Argentina, and Mexico, patients who improved after 6 months of either high-dose CYC or MMF were randomized to be maintained on either AZA 2 mg/kg/day or MMF 2 gm total daily dose. Prednisone up to 10 mg daily was permitted. Over 3 years of followup, MMF was statistically better than AZA in time to treatment failure (a composite including death, end-stage renal disease, doubling of serum creatinine, and renal flare), and in each element of the composite score. Severe adverse events occurred in significantly more patients receiving AZA than receiving MMF. In the smaller study (45), with sites in Western and Southern Europe, all patients receiving low-dose CYC, regardless of initial response, were randomized for maintenance therapy with either AZA, with a goal of 2 mg/kg/day, or MMF, with a goal of 2 gm/day. Over a period of 4 years there were no statistically significant differences in any outcome measures, including death, renal flares, end-stage renal disease, or doubling of serum creatinine. The Task Force Panel did not vote on the rate of medication taper during the maintenance phase; to date, there are no adequate data to inform the physician regarding how rapidly AZA or MMF can be tapered or withdrawn.

VIII. Recommendations for Changing Therapies in Patients Who Do Not Respond Adequately to Induction Therapy

In patients who fail to respond after 6 months of treatment (based on the treating physician's clinical impression) with glucocorticoids plus MMF or CYC, the Task Force Panel recommends a switch of the immunosuppressive agent from either CYC to MMF, or from MMF to CYC, with these changes accompanied by IV pulses of glucocortico-

ids for 3 days (level C evidence) (Figure 2). For CYC, either low dose or high dose can be used in white individuals, as discussed above in section IV. Evidence to support these opinions is not as strong as evidence for the efficacy of initial induction therapy. *The panel also voted that in some cases rituximab (61–65) can be used in patients whose nephritis fails to improve or worsens after 6 months of one induction therapy, or after the patient has failed both CYC and MMF treatments (level C evidence).* The Task Force Panel did not reach consensus regarding the use of calcineurin inhibitors in this setting; however, there is evidence for their efficacy as an induction agent and in refractory disease (65,66).

There is evidence in open-label trials (61,62) that LN may respond to rituximab treatment. Prospective, randomized, placebo-controlled trials did not show a significant difference between rituximab and placebo (on a background of MMF and glucocorticoids) after 1 year of treatment (63,64).

Evidence to support the use of cyclosporine or tacrolimus in LN is from open trials and recent prospective clinical trials (65–69); additional prospective trials are in progress. In a recent prospective trial (68), tacrolimus was equivalent to high-dose IV CYC in inducing complete and partial remissions of LN over a 6-month period. In another 4-year-long prospective trial (65), cyclosporine was similar to AZA in preventing renal flares in patients receiving maintenance therapy.

If nephritis is worsening in patients treated for 3 months with glucocorticoids plus CYC or MMF, the Task Force Panel recommended that the clinician can choose any of the alternative treatments discussed (level C evidence). Although combinations of MMF and calcineurin inhibitors (67) and of rituximab and MMF are being studied and might be considered for those who have failed the recommended induction therapies, data are not robust enough at this time to include them for voting scenarios.

Belimumab (anti-BLyS/BAFF), a recently FDA-approved treatment for SLE, has not been studied in LN. Patients with active SLE (Systemic Lupus Erythematosus Disease Activity Index score ≥ 6 , excluded if there was severe active nephritis) received IV belimumab or placebo in addition to glucocorticoids and an immunosuppressive agent (70,71). A significantly higher proportion of patients improved in the 10 mg/kg/month belimumab group compared to the placebo group after 52 weeks of treatment. Although not designed to evaluate LN, 14–18% of subjects had >2 gm of proteinuria per 24 hours at baseline. In a post hoc analysis, there were trends toward reduction in proteinuria at 53 weeks ($P = 0.0631$) and renal flares in the belimumab 10 mg/kg group ($P = 0.03$) (72). The FDA has approved belimumab for use in seropositive patients with SLE who have active disease in spite of prior therapies.

IX. Identification of Vascular Disease in Patients With SLE and Renal Abnormalities

Several types of vascular involvement can occur in renal tissue of SLE, including vasculitis, fibrinoid necrosis with narrowing of small arteries/arterioles (“bland” vasculopa-

thy), thrombotic microangiopathy, and renal vein thrombosis. In general, vasculitis is treated similarly to the more common forms of LN discussed above. Bland vasculopathy is highly associated with hypertension; it is not clear which comes first, SLE or hypertension. Thrombotic microangiopathy can be associated with a thrombotic thrombocytopenia-like picture. *The Task Force Panel recommended that thrombotic microangiopathy be treated primarily with plasma exchange therapy (level C evidence) (73).*

X. Treatment of LN in Patients Who Are Pregnant

The Task Force Panel recommended several approaches for management of LN in women who are pregnant (all level C evidence) (Figure 4). In patients with prior LN but no current evidence of systemic or renal disease activity, no nephritis medications are necessary. Patients with mild systemic activity may be treated with HCQ; this probably reduces activity of SLE during pregnancy (74). If clinically active nephritis is present, or there is substantial extra-renal disease activity, the clinician may prescribe glucocorticoids at doses necessary to control disease activity, and if necessary AZA can be added (75). High-dose glucocorticoid therapy in patients with SLE is associated with a high risk of maternal complications such as hypertension and diabetes mellitus (75). MMF, CYC, and methotrexate should be avoided because they are teratogenic in humans (Micromedex, searched April 2011). Although AZA is listed as pregnancy category D in Micromedex, cross-sectional studies have shown that the risk of fetal abnormalities is low (75). The dose of AZA should not exceed 2 mg/kg in a pregnant woman. For patients with a persistently active nephritis with documented or suspected class III or IV with crescents, consideration of delivery after 28 weeks for a viable fetus is recommended.

XI. Monitoring Activity of LN

Recommendations for monitoring LN are shown in Table 3, and result from votes of the Task Force Panel (level C evidence). Recommendations for monitoring the drugs/biologics used to treat LN have been reviewed elsewhere (76).

Discussion

This report, developed using validated guidelines methodology, represents the ACR recommendations for the case identification, treatment, and monitoring of LN. The previous guidelines presented a more general approach to SLE, whereas these recommendations focus specifically on nephritis and include medications not routinely in use at the time of the earlier publication. They include data on newer therapeutic modalities such as MMF, MPA, and rituximab, and address special situations such as pregnancy. Limitations of this report include the absence of an agreement on definitions of terms such as remission, flare, and response. Data also are unable at this time to support specific recommendations for steroid dosing and tapering of immunosuppressive regimens. While new therapies are being developed for lupus, results of their use in nephritis

Table 3. Recommended monitoring of lupus nephritis*

	Blood pressure	Urinalysis	Protein/creatinine ratio	Serum creatinine	C3/C4 levels	Anti-DNA
Active nephritis at onset of treatment	1	1	1	1	2†	3
Previous active nephritis, none currently	3	3	3	3	3	6
Pregnant with active GN at onset of treatment	1	1	1	1	1	1
Pregnant with previous nephritis, none currently	1	1	3	3	3	3
No prior or current nephritis	3	6	6	6	6	6

* Values are the monthly intervals suggested as the minimum frequency at which the indicated laboratory tests should be measured in the systemic lupus erythematosus scenarios shown in the left-hand column. GN = glomerulonephritis.
† Opinion of authors based on a study (51) published after the Task Force Panel had voted.

have not been published. These remain areas that warrant active investigation to further improve outcomes in lupus glomerulonephritis and future updates of these recommendations.

Nephritis remains one of the most devastating complications of lupus, with the incidence of end-stage renal disease due to lupus increasing between 1982 and 1995, without any decline seen by 2004. This poor outcome has occurred despite the availability of new therapeutic regimens (77,78). Standardized incidence rates for end-stage renal disease in the US have risen for younger patients, among African Americans, and in the South (79). We hope that institution of these recommendations might lead to reductions in these trends. Furthermore, they may allow us to evaluate whether those who receive the recommended therapies are less likely to develop end-stage renal disease. We have come a long way since LN was associated with a near terminal prognosis. With these recommendations, we strive to further improve outcomes and decrease morbidity and mortality in SLE.

Addendum. Therapies that were approved after the original literature review are not included in these recommendations.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Hahn had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Hahn, McMahon, W. Dean Wallace, Daikh, Merrill, Daniel J. Wallace, Kafaja, Kamgar, Lau, Parikh, Peng, Rastogi, Chen, Grossman.

Acquisition of data. Hahn, McMahon, W. Dean Wallace, Daikh, FitzGerald, Karpouzas, Daniel J. Wallace, Yazdany, Ramsey-Goldman, Singh, Khalighi, Choi, Gogia, Kafaja, Kamgar, Lau, Martin, Parikh, Peng, Rastogi, Chen, Grossman.

Analysis and interpretation of data. Hahn, McMahon, W. Dean Wallace, Daikh, Merrill, Daniel J. Wallace, Yazdany, Ramsey-Goldman, Singh, Khalighi, Choi, Kamgar, Lau, Parikh, Peng, Rastogi, Chen, Grossman.

REFERENCES

- Dooley MA, Aranow C, Ginzler EM. Review of ACR renal criteria in systemic lupus erythematosus. *Lupus* 2004;13:857–60.
- Kasitanon N, Magder LS, Petri M. Predictors of survival in systemic lupus erythematosus. *Medicine (Baltimore)* 2006;85:147–56.
- Ward MM, Pyun E, Studenski S. Mortality risks associated with specific clinical manifestations of systemic lupus erythematosus. *Arch Intern Med* 1996;156:1337–44.
- Alarcon GS, McGwin G Jr, Petri M, Reveille JD, Ramsey-Goldman R, Kimberly RP. Baseline characteristics of a multi-ethnic lupus cohort: PROFILE. *Lupus* 2002;11:95–101.
- Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Gladman DD, et al. Mortality in systemic lupus erythematosus. *Arthritis Rheum* 2006;54:2550–7.
- Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine (Baltimore)* 2003;82:299–308.
- American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. Guidelines for referral and management of systemic lupus erythematosus in adults. *Arthritis Rheum* 1999;42:1785–96.
- Fitch K, Bernstein SJ, Aguilar MS, Burnand B. The RAND/UCLA Appropriateness Method user's manual. Santa Monica (CA): RAND; 2001.
- Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res (Hoboken)* 2010;62:1515–26.
- Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64:625–39.
- Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005;112:e154–235.

12. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–7.
13. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int* 2004;65:521–30.
14. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004;15:241–50.
15. Markowitz GS, D'Agati VD. The ISN/RPS 2003 classification of lupus nephritis: an assessment at 3 years. *Kidney Int* 2007;71:491–5.
16. Hiramatsu N, Kuroiwa T, Ikeuchi H, Maeshima A, Kaneko Y, Hiromura K, et al. Revised classification of lupus nephritis is valuable in predicting renal outcome with an indication of the proportion of glomeruli affected by chronic lesions. *Rheumatology (Oxford)* 2008;47:702–7.
17. Canadian Hydroxychloroquine Study Group. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. *N Engl J Med* 1991;324:150–4.
18. Fessler BJ, Alarcon GS, McGwin G Jr, Roseman J, Bastian HM, Friedman AW, et al, for the LUMINA Study Group. Systemic lupus erythematosus in three ethnic groups. XVI. Association of hydroxychloroquine use with reduced risk of damage accrual. *Arthritis Rheum* 2005;52:1473–80.
19. Pons-Estel GJ, Alarcon GS, McGwin G Jr, Danila MI, Zhang J, Bastian HM, et al, for the LUMINA Study Group. Protective effect of hydroxychloroquine on renal damage in patients with lupus nephritis: LXV, data from a multiethnic US cohort. *Arthritis Rheum* 2009;61:830–9.
20. Jung H, Bobba R, Su J, Shariati-Sarabi Z, Gladman DD, Urowitz M, et al. The protective effect of antimalarial drugs on thrombovascular events in systemic lupus erythematosus. *Arthritis Rheum* 2010;62:863–8.
21. Wallace DJ. Does hydroxychloroquine sulfate prevent clot formation in systemic lupus erythematosus? [letter]. *Arthritis Rheum* 1987;30:1435–6.
22. Mann JF, Bakris GL. Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults. 2011. URL: http://www.uptodate.com/contents/antihypertensive-therapy-and-progression-of-nondiabetic-chronic-kidney-disease-in-adults?source=see_link.
23. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008;148:30–48.
24. Agodoa LY, Appel L, Bakris GL, Beck G, Bourgoignie J, Briggs JP, et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA* 2001;285:2719–28.
25. Rosenson RS. ATP III guidelines for treatment of high blood cholesterol. 2011. URL: <http://www.uptodate.com/contents/atp-iii-guidelines-for-treatment-of-high-blood-cholesterol>.
26. McMahon M, Hahn BH, Skaggs BJ. Systemic lupus erythematosus and cardiovascular disease: prediction and potential for therapeutic intervention. *Expert Rev Clin Immunol* 2011;7:227–41.
27. Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009;20:1103–12.
28. Chan TM, Tse KC, Tang CS, Mok MY, Li FK. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. *J Am Soc Nephrol* 2005;16:1076–84.
29. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005;353:2219–28.
30. Ong LM, Hooi LS, Lim TO, Goh BL, Ahmad G, Ghazalli R, et al. Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. *Nephrology (Carlton)* 2005;10:504–10.
31. Touma Z, Gladman DD, Urowitz MB, Beyene J, Uleryk EM, Shah PS. Mycophenolate mofetil for induction treatment of lupus nephritis: a systematic review and metaanalysis. *J Rheumatol* 2011;38:69–78.
32. Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, et al, for the ALMS Group. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med* 2011;365:1886–95.
33. Weng MY, Weng CT, Liu MF. The efficacy of low-dose mycophenolate mofetil for treatment of lupus nephritis in Taiwanese patients with systemic lupus erythematosus. *Clin Rheumatol* 2010;29:771–5.
34. Dooley MA, Hogan S, Jennette C, Falk R, for the Glomerular Disease Collaborative Network. Cyclophosphamide therapy for lupus nephritis: poor renal survival in black Americans. *Kidney Int* 1997;51:1188–95.
35. Isenberg D, Appel GB, Contreras G, Dooley MA, Ginzler EM, Jayne D, et al. Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. *Rheumatology (Oxford)* 2010;49:128–40.
36. Hardinger KL, Hebbard S, Bloomer T, Murillo D. Adverse drug reaction driven immunosuppressive drug manipulations: a single-center comparison of enteric-coated mycophenolate sodium vs. mycophenolate mofetil. *Clin Transplant* 2008;22:555–61.
37. Martindale database, “Mycophenolate.” In: *Micromedex* 20. 2011.
38. Lertdumrongluk P, Somparn P, Kittanamongkolchai W, Trait-anon O, Vadcharavivad S, Avihingsanon Y. Pharmacokinetics of mycophenolic acid in severe lupus nephritis. *Kidney Int* 2010;78:389–95.
39. Contreras G, Pardo V, Leclercq B, Lenz O, Tozman E, O'Nan P, et al. Sequential therapies for proliferative lupus nephritis. *N Engl J Med* 2004;350:971–80.
40. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, de Ramon Garrido E, Danieli MG, et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. *Ann Rheum Dis* 2010;69:61–4.
41. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, de Ramon Garrido E, Danieli MG, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002;46:2121–31.
42. Austin HA III, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, et al. Therapy of lupus nephritis: controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986;314:614–9.
43. Gourley MF, Austin HA III, Scott D, Yarboro CH, Vaughan EM, Muir J, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis: a randomized, controlled trial. *Ann Intern Med* 1996;125:549–57.
44. Steinberg AD, Steinberg SC. Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. *Arthritis Rheum* 1991;34:945–50.
45. Houssiau FA, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Petrovic R, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. *Ann Rheum Dis* 2010;69:2083–9.
46. Mok CC, Ho CT, Chan KW, Lau CS, Wong RW. Outcome and prognostic indicators of diffuse proliferative lupus glomerulonephritis treated with sequential oral cyclophosphamide and azathioprine. *Arthritis Rheum* 2002;46:1003–13.
47. Mok CC, Ho CT, Siu YP, Chan KW, Kwan TH, Lau CS, et al. Treatment of diffuse proliferative lupus glomerulonephritis: a comparison of two cyclophosphamide-containing regimens. *Am J Kidney Dis* 2001;38:256–64.
48. Yee CS, Gordon C, Dostal C, Petera P, Dadonien J, Griffiths B,

- et al. EULAR randomised controlled trial of pulse cyclophosphamide and methylprednisolone versus continuous cyclophosphamide and prednisolone followed by azathioprine and prednisolone in lupus nephritis. *Ann Rheum Dis* 2004;63:525–9.
49. Illei GG, Austin HA, Crane M, Collins L, Gourley MF, Yarboro CH, et al. Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis. *Ann Intern Med* 2001;135:248–57.
 50. Grootsholten C, Bajema IM, Florquin S, Steenberg EJ, Peutz-Kootstra CJ, Goldschmeding R, et al, for the Dutch Working Party on Systemic Lupus Erythematosus. Treatment with cyclophosphamide delays the progression of chronic lesions more effectively than does treatment with azathioprine plus methylprednisolone in patients with proliferative lupus nephritis. *Arthritis Rheum* 2007;56:924–37.
 51. Grootsholten C, Ligtgenberg G, Hagen EC, van den Wall Bake AW, de Glas-Vos JW, Bijl M, et al. Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis: a randomized controlled trial. *Kidney Int* 2006;70:732–42.
 52. Dall'Era M, Stone D, Levesque V, Cisternas M, Wofsy D. Identification of biomarkers that predict response to treatment of lupus nephritis with mycophenolate mofetil or pulse cyclophosphamide. *Arthritis Care Res (Hoboken)* 2011;63:351–7.
 53. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, de Ramon Garrido E, Danieli MG, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. *Arthritis Rheum* 2004;50:3934–40.
 54. Mersereau J, Dooley MA. Gonadal failure with cyclophosphamide therapy for lupus nephritis: advances in fertility preservation. *Rheum Dis Clin North Am* 2010;36:99–108.
 55. Boumpas DT, Austin HA III, Vaughan EM, Yarboro CH, Klippel JH, Balow JE. Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. *Ann Intern Med* 1993;119:366–9.
 56. Somers EC, Marder W, Christman GM, Ognenovski V, McCune WJ. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. *Arthritis Rheum* 2005;52:2761–7.
 57. Yu F, Tan Y, Liu G, Wang SX, Zou WZ, Zhao MH. Clinicopathological characteristics and outcomes of patients with crescentic lupus nephritis. *Kidney Int* 2009;76:307–17.
 58. Tang Z, Yang G, Yu C, Yu Y, Wang J, Hu W, et al. Effects of mycophenolate mofetil for patients with crescentic lupus nephritis. *Nephrology (Carlton)* 2008;13:702–7.
 59. Radhakrishnan J, Moutzouris DA, Ginzler EM, Solomons N, Siempos II, Appel GB. Mycophenolate mofetil and intravenous cyclophosphamide are similar as induction therapy for class V lupus nephritis. *Kidney Int* 2010;77:152–60.
 60. Austin HA III, Illei GG, Braun MJ, Balow JE. Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. *J Am Soc Nephrol* 2009;20:901–11.
 61. Jonsdottir T, Gunnarsson I, Mourao AF, Lu TY, van Vollenhoven RF, Isenberg D. Clinical improvements in proliferative vs membranous lupus nephritis following B-cell depletion: pooled data from two cohorts. *Rheumatology (Oxford)* 2010;49:1502–4.
 62. Terrier B, Amoura Z, Ravaud P, Hachulla E, Jouenne R, Combe B, et al. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. *Arthritis Rheum* 2010;62:2458–66.
 63. Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum* 2010;62:222–33.
 64. Rovin BH, Appel G, Furie R, Kamen D, Fervenza FC, Spindler A, et al. Effects of rituximab (RTX) on anti-dsDNA and C3 levels and relationship to response: results from the LUNAR Trial [abstract]. *J Am Soc Nephrol* 2009;20:406A.
 65. Moroni G, Doria A, Mosca M, Alberighi OD, Ferraccioli G, Todesco S, et al. A randomized pilot trial comparing cyclosporine and azathioprine for maintenance therapy in diffuse lupus nephritis over four years. *Clin J Am Soc Nephrol* 2006;1:925–32.
 66. Ogawa H, Kameda H, Nagasawa H, Sekiguchi N, Takei H, Tsuzaka K, et al. Prospective study of low-dose cyclosporine A in patients with refractory lupus nephritis. *Mod Rheumatol* 2007;17:92–7.
 67. Bao H, Liu ZH, Xie HL, Hu WX, Zhang HT, Li LS. Successful treatment of class V+IV lupus nephritis with multitarget therapy. *J Am Soc Nephrol* 2008;19:2001–10.
 68. Chen W, Tang X, Liu Q, Fu P, Liu F, Liao Y, et al. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: a multicenter randomized clinical trial. *Am J Kidney Dis* 2011;57:235–44.
 69. Miyasaka N, Kawai S, Hashimoto H. Efficacy and safety of tacrolimus for lupus nephritis: a placebo-controlled double-blind multicenter study. *Mod Rheumatol* 2009;19:606–15.
 70. Navarra SV, Guzman RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011;377:721–31.
 71. Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzova D, et al, for the BLISS-76 Study Group. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011;63:3918–30.
 72. Petri M. Belimumab for systemic lupus erythematosus [letter]. *Lancet* 2011;377:2080–1.
 73. Kaplan AA, George JN. Treatment of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome in adults. 2011. URL: <http://www.uptodate.com/contents/treatment-of-thrombotic-thrombocytopenic-purpura-hemolytic-uremic-syndrome-in-adults>.
 74. Clowse ME, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. *Arthritis Rheum* 2006;54:3640–7.
 75. Gordon C. Pregnancy and autoimmune diseases. *Best Pract Res Clin Rheumatol* 2004;18:359–79.
 76. Schmajuk G, Yazdany J. Drug monitoring in systemic lupus erythematosus: a systematic review. *Semin Arthritis Rheum* 2011;40:559–75.
 77. Ward MM. Changes in the incidence of end-stage renal disease due to lupus nephritis, 1982-1995. *Arch Intern Med* 2000;160:3136–40.
 78. Ward MM. Changes in the incidence of endstage renal disease due to lupus nephritis in the United States, 1996-2004. *J Rheumatol* 2009;36:63–7.
 79. Costenbader KH, Desai A, Alarcon GS, Hiraki LT, Shaykevich T, Brookhart MA, et al. Trends in the incidence, demographics, and outcomes of end-stage renal disease due to lupus nephritis in the US from 1995 to 2006. *Arthritis Rheum* 2011;63:1681–8.